Remarks

The present claims concern methods for identifying bacterial targets for antibacterial agents based on binding of an inhibitor polypeptide (or a fragment thereof) from a bacteriophage with a bacterial protein. Claims 100 and 115 were amended to specify that a bacterial protein is contacted with a bacteriophage polypeptide. (Support is provided for example, on p.45, lines 8-11.) Also Claims 100, 101, 102, 106, 107, 108, and 114 were amended to specify a polypeptide rather than an open reading frame product. (Support is provided, for example, on p.29, line 28.) The specification was amended to correct typographical errors and to more properly refer to the Qin reference on p.44. No new matter is added by these amendments.

Rejections under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 100-115, all the pending claims, under 35 U.S.C. 112, first paragraph as allegedly not providing enablement to make and/or use the invention commensurate in scope with the claims, raising particular objections with response to particular claims.

Applicant respectfully traverses these rejections as they may be considered in connection with the present claims.

Preliminarily, as indicated in connection with the rejections under 35 U.S.C. 112, first paragraph, Applicant has amended the claims to refer to a "polypeptide" rather than an "open reading frame product". Thus, Applicant respectfully submits that the Examiner's objections concerning the meaning of the term "open reading frame product" or "ORF product" are obviated.

The Examiner's rejections and associated comments allege that the disclosure is not enabling for the breadth of claims, continuing on with allegations concerning lack of enablement for particular claims. Unfortunately, the Examiner did not demonstrate in what way the disclosure is not enabling or show why one of ordinary skill in the art would not be able to carry out the claimed invention without undue experimentation. Indeed, it appears that the Examiner would require a cookbook description for each possible assay and detailed structural information for each possible bacteriophage-encoded inhibitor polypeptide and for each bacterial target. Such a view is unsuitable for the subject matter claimed, ignoring the general applicability of methods,

the standard technical knowledge possessed by one of ordinary skill in the art, and the guidance provided in the present specification. The Examiner's conclusory statements do not provide the clear explanation supported by evidence required by the Federal Circuit to support the rejection of the claims.

Quite to the contrary, the enablement of the present claims is demonstrated by results obtained by practicing the claimed methods as described in U.S. Patent 6,376,652 (having the same inventors as the present invention). The '652 patent describes the identification of a bacterial target using an inhibitory bacteriophage polypeptide. A copy of the '652 patent is attached for the Examiner's convenience. One of ordinary skill in the art will recognize that the work described in the '652 patent can also be applied to other inhibitory bacteriophage polypeptides and other bacterial target proteins, and the Examiner has provided nothing to support a contrary conclusion. Thus, Applicant respectfully submits that the full scope of the present claims is enabled.

Applicant respectfully requests that the Examiner reconsider the present claims and the specification in view of the description provided in the '652 patent, that demonstrates that the invention specified in the pending claims can be carried out as described in the present specification.

If, after reviewing the present response and the '652 patent, the Examiner does not believe that the present claims are enabled, Applicant respectfully requests that the Examiner provide a reasonable explanation supported by evidence of why one of ordinary skill in the art would be unable to carry out the claimed invention without undue experimentation.

As the various points raised by the Examiner concerning alleged lack of enablement in connection with particular claims is addressed generally by the description provided in the '652 patent in view of the guidance provided in the present specification, Applicant does not separately address the Examiner's detailed objections, except as shown below.

Claims 100 and 106

The Examiner alleged that the specification failed to describe a step of contacting ORF product with the bacterial target and no indication has been given as to how the step of identifying is accomplished.

Applicant submits that contacting the ORF product with the bacterial target is inherent in the "determining" step specified. In addition, "contacting" is implicit in "binding", as binding cannot occur without such contact. In order to make this explicit, claim 100 is amended to now specify contacting a bacterial protein (generally a crude mixture of bacterial proteins) with an inhibitory bacteriophage polypeptide. In addition, the precise technique used for identification of the target was not specified, as a variety of different identification methods can be used. This amendment does not alter the scope of the claim.

The Examiner also objected to the reference to the parent application 09/407,804 at page 8, lines 4-8, stating that Applicants assert that identification of these inhibitory ORFs is described in patent application 09/407,804. The Examiner asserted that this incorporation by reference is found improper, but does not explain why it should be improper.

To the contrary, Applicant does not believe that the incorporation by reference is improper. The application specified is a parent application, and the statement that the identification of the particular inhibitory polypeptides was described in that application merely indicates an additional public description of those inhibitory polypeptides. In fact, that earlier description is not necessary, because the description of the six inhibitory polypeptides from phage 77 is also included in the present specification (see Figures, Tables 3 & 4, and Examples in the specification).

Thus, Applicant respectfully submits that reference to the parent application is proper and requests that the Examiner reconsider and withdraw this objection.

For Claim 106 the Examiner also asserted that the claim is further directed to identification of a bacterial nucleic acid sequence encoding a polypeptide target of the bacteriophage inhibitor protein, and that it is not clear how identification of nucleic acid results from identification of protein.

Applicant submits that claim 106 was clear in specifying identification of the nucleic acid encoding the bacterial target as an additional step, by specifying that the identifying "further comprises identifying a bacterial nucleic acid sequence encoding a polypeptide target of said bacteriophage inhibitor protein". Nonetheless, to address the Examiner's comment, claim 106 is amended to specify that "the method" includes identification of the bacterial nucleic acid sequence. This amendment does not alter the scope of the claim.

Rejections under 35 USC 112, 1st paragraph

The Examiner rejected claims 100-114 under 35 USC 112, 1st paragraph as allegedly being indefinite. The Examiner objected to use of the term "bacteriophage open reading frame product" or "ORF product", and to the term "ORF". Applicant respectfully traverses these rejections.

As pointed out in the specification, both mRNAs and polypeptides are open reading frame products, and each can be biologically active. Thus, either can be an inhibitory ORF product. However, recognizing that it is much more common for polypeptides to be the inhibitory species, Applicant has amended the claims to specify "polypeptide". Likewise, the term "ORF" has attained such common usage as to be a common term in its own right, and not just an acronym. However, because the Examiner has raised the objection, Applicant has replaced the term with the phrase, "open reading frame". Thus, Applicant submits that the Examiner's objections are obviated, and requests that the Examiner withdraw the rejection. These amendments do not alter the scope of the claims.

In view of the comments above and the attached U.S. Patent 6,376,652, Applicant respectfully requests that the Examiner reconsider and withdraw the outstanding rejections, and allow the present claims.

If at any time a telephone interview would be helpful to advance prosecution, the Examiner is invited to telephone the undersigned at (858) 847-6714.

A Notice of Appeal and the fee for that notice accompanies this Amendment. No additional fee is believed due in connection with this communication. However, if any additional fee is due, of if the amount submitted is incorrect, kindly charge or credit the appropriate amount to Deposit Account 50-0872.

Respectfully submitted,

Date 12 June 2002

By _____

FOLEY & LARDNER
402 West Broadway
23rd Floor
San Diego, California 92101-3542
Telephone: (619) 230-6528- 234-6655
Facsimile: (619) 234-3510

Wesley B. Ames
Attorney for Applicant
Registration No. 40,893

Appendix 1: Clean copy of substitute amended claims

100. (Amended) A method for identifying at least one target for antibacterial agents, comprising

contacting a bacterial protein with a bacteriophage polypeptide that inhibits bacterial growth;

determining whether said bacteriophage polypeptide binds to said bacterial protein; and

identifying any said bacterial protein bound by said bacteriophage polypeptide wherein binding of said bacteriophage polypeptide to said bacterial protein is indicative that said bacterial protein is a said target.

101. (Amended) The method of claim 100, wherein said determining comprises identifying at least one bacterial protein which binds to said bacteriophage polypeptide using affinity chromatography on a solid matrix.

102. (Amended) The method of claim 100, wherein said determining comprises identifying at least one bacterial protein which binds to an active fragment of said bacteriophage polypeptide.

106. (Amended) The method of claim 100, wherein said method further comprises identifying a bacterial nucleic acid sequence encoding said target of said bacteriophage polypeptide.

107. (Amended) The method of claim 100, wherein said determining is performed for a plurality of bacteriophage polypeptides that inhibit bacterial growth.

108. (Amended) The method of claim 100, wherein said determining is performed using bacteriophage polypeptides that inhibit bacterial growth from a plurality of different bacteriophages.

114. (Amended) The method of claim 100, wherein said identifying further comprises identifying a fragment of said bacterial protein to which said bacteriophage polypeptide binds.

115. (Amended) A method for identifying at least one target for antibacterial agents, comprising

contacting at least one bacteriophage protein or fragment thereof that inhibits bacterial growth with a bacterial protein;

determining whether said bacteriophage protein or fragment interacts with a bacterial protein, using a means for determining whether said bacteriophage protein or fragment thereof binds with said bacterial protein; and

identifying any said bacterial protein bound by said bacteriophage protein or fragment,

wherein binding of said bacterial protein by said bacteriophage protein or fragment is indicative that said bacterial protein is a said target.

Appendix 2: Marked-up set of amended claims

100. (Amended) A method for identifying at least one target for antibacterial agents, comprising

contacting a bacterial protein with a bacteriophage polypeptide that inhibits bacterial growth;

determining whether [a] said bacteriophage polypeptide [open reading frame product that inhibits bacterial growth] binds to [a] said bacterial protein; and

identifying any said bacterial protein bound by said bacteriophage polypeptide [open reading frame product as a said target] wherein binding of said bacteriophage polypeptide to said bacterial protein is indicative that said bacterial protein is a said target.

101. (Amended) The method of claim 100, wherein said determining comprises identifying at least one bacterial protein which binds to said bacteriophage polypeptide [inhibitor protein] using affinity chromatography on a solid matrix.

102. (Amended) The method of claim 100, wherein said determining comprises identifying at least one bacterial protein which binds to an active fragment of said bacteriophage polypeptide [ORF product].

106. (Amended) The method of claim 100, wherein [identifying said bacterial protein] said method further comprises identifying a bacterial nucleic acid sequence encoding [a polypeptide] said target of said bacteriophage [inhibitor protein] polypeptide.

107. (Amended) The method of claim 100, wherein said determining is performed for a plurality of bacteriophage polypeptides that inhibit bacterial growth [open reading frame products].

108. (Amended) The method of claim 100, wherein said determining is performed using bacteriophage polypeptides that inhibit bacterial growth [open reading frame products] from a plurality of different bacteriophages.

114. (Amended) The method of claim 100, wherein said identifying further comprises identifying a fragment of said bacterial protein to which said bacteriophage polypeptide [open reading frame product] binds.

115. (Amended) A method for identifying at least one target for antibacterial agents, comprising

[providing] contacting at least one bacteriophage protein or fragment thereof that inhibits bacterial growth with a bacterial protein;

determining whether said bacteriophage protein or fragment interacts with a bacterial protein, using a means for determining whether said bacteriophage protein or fragment thereof binds with [a] said bacterial protein; and

identifying any said bacterial protein bound by said bacteriophage protein or fragment [as a said target],

wherein binding of said bacterial protein by said bacteriophage protein or fragment is indicative that said bacterial protein is a said target.

Appendix 3: Marked-up replacement paragraph

Paragraph at page 44, lines 5-28

The second approach is based on identifying protein:protein interactions between the phage ORF product and bacterial e.g., *S. aureus*[e.g.] proteins, using a biochemical approach based, for example, on affinity chromatography. This approach has been [used] described, for example, [to identify protein:protein interactions between lambda phage proteins and proteins from their E. coli host (] in Sopta, M., Carthew, R.W., and Greenblatt, J. (1985) *J. Biol. Chem.* 260, 10353-10369[)]. The phage ORF is fused to a peptide tag (*e.g.* glutathione-S-transferase ("GST"), 6xHIS ("HIS") and/or calmodulin binding protein ("CPB") within a commercially available plasmid vector that directs high level expression on induction of a suitably responsive promoter driving the fusion's expression. The translated fusion protein is expressed in *E. coli*, purified, and immobilized on a solid phase matrix via, for example, the tag. Total cell extracts from the host bacterium, *e.g.*, *S. aureus*, are then passed through the affinity matrix containing the immobilized phage ORF fusion protein; host proteins retained on the column are then eluted under different conditions of ionic strength, pH, detergents, etc., and characterized by gel electrophoresis and other techniques. Appropriate controls are run to guard against nonspecific binding to the resin. Target proteins thus recovered should be enriched for the phage protein/peptide of interest and are subsequently electrophoretically or otherwise separated, purified, sequenced, or biochemically analyzed. Usually sequencing entails individual digestion of the proteins to completion with a protease (*e.g.*,[-]trypsin), followed by molecular mass and amino acid composition and sequence determination using, for example, mass spectrometry, *e.g.*, by MALDI-TOF technology (Qin, J., Fenyo, D., Zhao, Y., Hall, W.W., Chao, D.M., Wilson, C.J., Young, R.A. and Chait, B.T. (1997). *Anal. Chem.* 69:3995-4001).